ANIMAL HEALTH INSTITUTE

Representing manufacturers of animal health products

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December 3, 2004

Division of Dockets Management
U.S. Food and Drug Administration
HFA-305
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 2003D-0380 Guidance for Industry: Process Analytical Technology – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

The ANIMAL HEALTH INSTITUTE ("AHI") submits these comments on Guidance for Industry, "Process analytical Technology – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance" published as final guidance by FDA in the *Federal Register* on October 4, 2004.

AHI is the national trade association representing manufacturers of animal health products – the pharmaceuticals, vaccines and feed additives used in modern food production, and the medicines that keep livestock and pets healthy.

Since this document was written in a broad, general, noncommittal way, our comments are broad in nature. There were not really any specific issues of guidance in the document, but it was more philosophical in nature. This philosophical approach was addressed (admitted) in the introduction.

Our concern is that the philosophy expounded in the document is not consistent with the approach CVM has been using to review files. The document is highly academic and does not address the practical resource issues faced by a firm. Throughout the document they refer to standards developed outside of FDA such as ASTM International. Our experience is that CVM does not accept standards that are not part of the FDA framework. For example when working with irradiation, we have been forced to follow standard pharmaceutical validation procedures and not reference ISO or NRC regulations. We have been asked to provide validation data on instrumentation that is developed and validated outside our industry. Bringing in novel instrumentation has the potential of starting a long series of negotiations on acceptable validation approaches which tend to drag on through several iterations.

The guidance goes on to talk about mathematical and statistical approaches to predicting product performance, this being done in real time. We find it difficult to believe that the Agency

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will accept real time statistical evaluation of data for product release when they do not accept a statistical approach to sterility validation with static data that can be evaluated over time.

The philosophy of PAT that validating the materials and processes in the manufacture of a drug formulation will obviate the need for end testing is contrary to what history has shown. Firms are required to provide process validation of the sterilization process used in the manufacture of sterile products. Firms are required to have real time environmental monitoring, real time monitoring of sterilizers (autoclaves), completely validated processes for sterilizing equipment and products, yet a sterility test is required to release goods. And this is one of the most scrutinized sections of a drug application. The fear is that PAT will add this same additional level of validation requirements to processes now employed in non-sterile technologies, and industry will still have to meet end testing requirements.

The document discusses validating in-process measurements; this is another level of validation added to the development process. The document speaks of parametric release. The experience of our members is that they have validated terminal sterilization cycles, yet are still required to run sterility testing. The same product is parametrically released for Europe.

The document speaks to the idea of generating research data on marketed product with a PAT tool. It says that it will view such data as R&D data and that inspections would treat it as R&D while only holding the firm to the current regulatory standards. I am uncomfortable with that statement. Our members' experience has been that the Agency takes the most conservative path. They have seen them extrapolate R&D data and deny real time GMP data for calculating expiry in complex formulations. PAT would be applied to complex formulations which is an area the Agency is uncomfortable with. When the comfort level in CVM is low, they take the conservative approach.

Now that we have discussed the philosophical differences between the document as written and real practice, AHI would suggest the following specific comments and questions.

- The tone of the guidance is not specific enough to give industry a clear understanding of what is acceptable under PAT. What level of validation is expected? Can end testing be eliminated? If firms do not report changes justified under PAT, how will files be reconciled with practice?

- How will the Agency approve a mathematical/statistical approach to quality in real time?

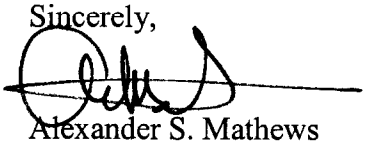
- PAT seems to add another layer of validation to processes that are regulated by product testing. This seems to mirror sterility validation which is very extensive, yet product testing is still required. This would make the files more complex with questionable added value.

- How will conflicts be resolved when a firm releases product to the market with changes determined by the firm not to be reportable based on PAT, but the Agency

may not agree with the assessment if they had opportunity to review the data. This would come to light in an inspection, and product manufactured could be subject to Agency action.

AHI appreciates the opportunity to provide input on this document for consideration by the Agency.

Sincerely,



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